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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,333	VOYTA ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-11,14-31 and 34-45* is/are pending in the application.

4a) Of the above claim(s) *34-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6, 8-11, 14-31, 39-45* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/14/07 has been entered.

2. Claims 2 and 32-33 were canceled by the amendment. Claims 1, 3-6, 8-11, 14-31, and 34-45 are pending in the application, with claims 34-38 currently withdrawn.

Terminal Disclaimer

3. The terminal disclaimer filed on 9/26/06 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of **10/462,742** has been reviewed and is accepted. The terminal disclaimer has been recorded.

Information Disclosure Statement

4. Applicant's Information Disclosure Statement filed 3/14/07 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

5. The US patent documents **2004/059182** and **6,582,503 B1** not been considered because they appear to be incorrect citations. The document numbers given do not correspond with the listed dates, names or class/subclass information listed for the documents.

6. US Patent **6,905,826 B2** (Ferea et al.) has been lined through to avoid duplicate citation because the document is already of record.

Objections/Rejections Withdrawn

6. The provisional rejections of claims 1-6, 8-11, 14-33 and 39-45 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending Application No. 10/462,742 are withdrawn in light of the above-mentioned terminal disclaimer filed on 9/26/06.

7. The rejections of claims 1-6, 8-11, 14-33 and 39-45 under 35 USC 112, 2nd paragraph as set forth in the previous Office action have been obviated by the amendments.

8. The rejections of claims 1, 3-6, 9-11, 15-26, and 28-32 under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. have been withdrawn in response to the amendments to incorporate limitations of claim 2 into the independent claim.

9. The rejections of claims 1, 9-10, 23-26, 28-29, and 32-33 under 35 U.S.C. 103(a) as being unpatentable over Bers et al. in view of Fodor et al. are similarly withdrawn in response to the amendments to incorporate limitations of claim 2 into the independent claim.

Claim Objections

10. Claim 11 is objected to because of the following informalities: the last 5 lines of the claim refer to "**a** first enzyme conjugate" and "**a** second enzyme conjugate", which apparently refers back to the first and second enzyme conjugates that are mentioned previously in the claim (and also in claim 1). If the same first and second enzyme conjugates are being referred to, it is suggested that the later references should refer to "the" or "said" first and second enzyme conjugates (rather than "a") in order to avoid confusion.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 3-6, 8-11, 14-31, and 39-45 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

13. Claim 1 as amended recites a "**two-dimensional** solid support". Applicant's reply (see page 9) states that support for the amendments may be found in the specification at p. 14, line 12, which discloses:

> The solid support surface may be two-dimensional (i.e., substantially planar). Alternatively, the support surface may be non-planar.

However, it is noted that the specification passage above refers only to the *surface* of the support as being two-dimensional. By contrast, the claim now conveys that the *support,* rather than the *surface* of the support, is two-dimensional. This represents new matter because the disclosure of a solid support having a *surface* that is two-dimensional differs in scope from the currently claimed methods involving a solid support that itself is two-dimensional (i.e., where the entire solid support is two-dimensional).

14. Claim 11 as amended recites that "**wherein contacting the surface layer of the solid support with the sample results in at least some of the probes being bound to a first enzyme conjugate comprising the first enzyme and at least some the probes being bound to a second enzyme conjugate comprising the first enzyme**". Applicant's reply does not indicate where support could be found for such limitations. The specification does not provide blaze marks nor direction for the instant methods encompassing the above-mentioned limitations, as currently recited. The specification mentions target molecules being labeled with first and second enzymes, or alternatively with moieties capable of binding to the first and second enzyme conjugates (see page 5), but there is no clear description in the specification of the currently claimed subject matter wherein sample application results in the probes being bound to the first and second enzyme conjugates.

In particular, one skilled in the art cannot envisage possession of such methods as currently claimed because it is unclear how contacting the solid support with a sample in which the target molecules are *indirectly* labeled with moieties capable of binding to the enzyme conjugates (as in lines 8-10 of the claim) could result in the probes on the support becoming bound to the enzyme conjugates (see also rejection under 112, 2nd paragraph below).

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 as amended recites that either:

> ...the first target molecules are labeled with the first enzyme to form the first enzyme conjugate and the second target molecules are labeled with the second enzyme to form the second enzyme conjugate; **or**
>
> ...the first target molecules are labeled with a moiety capable of binding to the first enzyme conjugate and the second target molecules are labeled with a moiety capable of binding to the second enzyme conjugate; **and**
>
> wherein contacting the surface layer of the solid support with the sample results in at least some of the probes being bound to a first enzyme conjugate comprising the first enzyme and at least some the probes being bound to a second enzyme conjugate comprising the first enzyme *(emphasis added)*

The claim is indefinite because it is unclear how contacting the sample with the solid support would have the effect of causing some of the probes to become bound to the first and second enzyme conjugates in the case of lines 4-6 above. In such a case, the target molecules are labeled indirectly with a moiety *capable of binding* to the first and second enzyme conjugates. However, there is no requirement that the enzyme conjugates are actually present in the sample. As such, it is not clear how applying the sample with the target molecules would cause the probes on the support to become bound to the enzyme conjugates.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1, 3-6, 9-11, 14-26, 28-31, 39-40, and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. (US 4,931,223) in view of Fodor et al. (US 6,309,822 B1) and Voyta et al. (US 5,145,772).

Bronstein et al. teach a method of detecting chemiluminescent emissions on a solid support (coated matrix such as a nylon membrane), comprising contacting a surface layer of the solid support with a substrate composition that is a mixture of two or more enzymatically cleavable chemiluminescent substrates that are capable of being activated (cleaved) by different enzymes (see in particular the abstract; column 1, line 53 to column 3, line 3; column 7, lines 5-19; column 8, lines 1-21; Examples I-II; and claim 17 in particular). The signals produced by the two chemiluminescent substrates are then detected either simultaneously or sequentially (column 2, line 11; column 8, lines 16-21 and 42-65; column 11, lines 3-19). Bronstein et al. further teach that a plurality of probes may be immobilized in discrete areas ("spots") on the solid support (see column 8, lines 1-7; column 10, lines 29-36; column 11, lines 15-18; column 13, lines 5-18). The probes may be capture antibodies as in Example I or nucleic acid probes as in Example II (see also column 2, line 64 to column 3, line 3). At least some of the probes are bound to a first enzyme conjugate comprising the first enzyme, and at least some of the probes are bound to a

second enzyme conjugate comprising the second enzyme (see the above passages and especially column 8, lines 1-21).

Bronstein et al. differs from the claimed invention in that it fails to specifically teach that the plurality of probes are immobilized in the discrete areas *at a density of at least 50 discrete areas per cm2*. The reference also fails to specifically teach that the two-substrate composition is contacted with the solid support in the presence of a *composition comprising an onium polymer or copolymer chemiluminescent quantum yield enhancing material.*

Fodor et al. teach high density probe arrays, in which greater than about 400,000 different probes can be immobilized per cm2 (see in particular the abstract; column 2, lines 33-43; column 3, lines 18-48). The high-density probe arrays can be used to detect and quantify target nucleic acid sequences and/or to monitor the expression of a multiplicity of genes (column 33, lines 20-31; column 5, lines 34-36; column 6, lines 23-35; column 2, lines 53-61). Fodor et al. teach that the high density probe arrays offer several advantages, including reduced intra- and inter-array variability, increased information content, and higher signal-to-noise ratio (see column 12 to column 15, line 60). In particular, Fodor et al. note that the arrays have advantages over blotted arrays (which is the technique used in Bronstein et al.), such as significantly higher hybridization efficiencies (column 14, line 61 to column 15, line 12). The probe arrays of Fodor et al. are two-dimensional (see for example column 10, lines 21-24).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the high density probe arrays of Fodor et al. as the solid support in the method of detecting chemiluminescent emissions of Bronstein et al. in order to allow for increased information content and massively parallel processing of hybridization data, reduction of assay variability,

and/or to detect and quantify a multiplicity of genes with increased information content and sensitivity.

One would have a reasonable expectation of success in using the solid support of Fodor et al. in the method of detecting chemiluminescent emissions of Bronstein et al. because Fodor et al. teach that the microarrays may be used in methods employing chemiluminescent detection (column 49, lines 5-12, column 82, lines 43-65) and also that enzyme labels may be used (column 20, lines 51-61). One would also have a reasonable expectation of success because Fodor et al. teach that the solid support may be a nylon membrane (column 95, lines 49-57), which is the same material used as the solid support by Bronstein et al. One would also have a reasonable expectation of success because Bronstein et al. teach that the chemiluminescent detection method can be used in any art-recognized immunoassay, chemical assay, or nucleic acid probe assay technique (column 2, lines 54-68).

It is noted, however, that the combination of Bronstein et al. and Fodor et al. differs from the claimed invention in that the references fail to specifically teach that the two-substrate composition is contacted with the solid support in the presence of a *composition comprising an onium polymer or copolymer chemiluminescent quantum yield enhancing material.*

Voyta et al. teach that enhancement agents such as polymeric quaternary onium (amm**onium**) salts (e.g. poly(vinyl-benzyltrimethylammonium) act as enhancement agents in chemiluminescent assays by stabilizing light-emitting fluorophores, allowing for greater signal intensity (see the abstract; column 2, lines 45-64; column 5, line 17 to column 6, line 45; and Table I in particular). Voyta et al. teach that the enhancement agent may be simply added to the chemiluminescent substrate composition (column 13, lines 10-17), such that the

chemiluminescent substrate composition would be contacted with the solid support in the presence of the enhancement agent. Other water-soluble oligomeric, homopolymeric, and copolymeric materials can be used as enhancers in addition to or instead of quaternary ammonium polymers (column 5, line 65 to column 6, line 45). These include polyacids and salts thereof, polyvinyl alcohol, and synthetic polypeptides.

Therefore, it would have been obvious to include an enhancement agent such as a quaternary onium polymer at the same time the two-substrate composition is contacted with the sample (and therefore with the solid support) as taught by Voyta in the method of detecting chemiluminescent emissions of Bronstein et al. and Fodor et al. in order to enhance the chemiluminescent signals.

With respect to claims 3-6, Fodor et al. teach that in addition to test probes, the array can include control probes or normalization controls, which can serve to calculate a background signal and to allow for quantification of unknowns, or as expression level controls (column 14, lines 28-35; column 4, lines 6-12; column 9, lines 6-46; column 19, lines 14-21; column 22, line 57 to column 24, line 39; and column 35, line 29 to column 36, line 61). The control probes can be localized at any position in the array or at multiple positions throughout the array (column 23, lines 20-23). The intensity of the second (unknown) signal is quantified by comparing the signal intensity to that of mismatch control and/or background signal intensity (column 24, lines 9-15; column 26, lines 10-25). The signals are detected by detecting the signal strength at each location (representing a different probe) on the array (column 35, lines 29-44).

With respect to claim 9, Bronstein et al. teach detecting the location of the signals on the solid support in that the brightness of the spots are visualized (see for example column 11, lines 15-19).

With respect to claim 10, Bronstein et al. teach nucleic acid probes (column 2, line 64 to column 3, line 3).

With respect to claim 11, Bronstein et al. teach contacting the solid support with a solution containing first target molecules labeled with the first enzyme (anti-beta-HCG antibodies conjugated to alkaline phosphatase) and second target molecules labeled with the second enzyme (anti-HLH antibodies conjugated to carboxylesterase) to form "enzyme conjugates" (Example I). When these target molecules become bound to the probes on the solid support, the probes thereby also become bound to the enzyme conjugates.

Fodor et al. also teach samples comprising target nucleic acids, in which the targets may be labeled with enzymes (column 20, line 28 to column 21, line 24). Different targets may be labeled with different labels (column 81, lines 16-38). Fodor et al. teach that enzyme labels may be added to the target molecules prior to or after hybridizing with the immobilized probes--i.e., that the enzyme labels may be "direct" or "indirect" labels (column 20, line 51 to column 21, line 24). For example, Fodor et al. teach that target nucleic acids may be biotinylated, which allows them to be subsequently labeled with an avidin-conjugated label after the target nucleic acids are hybridized to the probes. As such, it would have been obvious to one of ordinary skill in the art to indirectly label the target molecules since Fodor et al. teach that both indirect and direct labeling are effective means of labeling target molecules.

With respect to claim 14, Fodor et al. teach that the target molecules may be pools of nucleic acids (column 2, line 62 to column 6, line 9). For example, the sample may comprise a first pool (total RNA pool) that is mixed or spiked with a second pool of 13 target RNAs (see column 103, line 45 to column 104, line 8). As another example, a sample including target pool of nucleic acids can be used together or "spiked" with a second pool of control nucleic acids (column 24, lines 22-39; column 9, lines 35-41; column 6, lines 36-63).

With respect to claims 15-16, Fodor et al. teach that the target nucleic acid sample may comprise mRNA transcripts or nucleic acids derived from mRNA transcripts, such as cDNA derived (reversed transcribed) from mRNA (column 17, line 47 to column 18, line 34; column 18, lines 35-54).

With respect to claim 17, Fodor et al. teach that the concentration of the target nucleic acids is proportional to the transcription level (and therefore expression level) of that gene (column 18, lines 9-34).

With respect to claims 18-22, Fodor et al. teach control probes as discussed above with respect to claim 3, and both Bronstein et al. and Fodor et al. each teach samples comprising target nucleic acids, in which the targets may be labeled with different enzymes as discussed above with respect to claims 11 and 13. The sample of Fodor et al. may include pools of nucleic acids that are mRNA transcripts or nucleic acids derived from mRNAs such as cDNA discussed above with respect to claim 14. Fodor et al. teach that the concentration of the target nucleic acids is proportional to the transcription level (and therefore expression level) of that gene as discussed above with respect to claim 17.

With respect to claims 23-26, Fodor et al. teach arrays with densities of 400,000 per cm2.

With respect to claims 28-29, Bronstein et al. teach that the first and second chemiluminescent substrates should emit light of different wavelengths (see for example the abstract), and that the signals are imaged using multiple filters that isolate the different signals from each of the chemiluminescent substrates (column 13, lines 43-52; column 8, lines 16-21).

With respect to claims 30 and 32, Bronstein et al. teach that the composition comprising the two chemiluminescent substrates includes carbonate buffer (see column 10, lines 48-54) and further that the chemiluminescent substrates are both 1,2-dioxetanes (see for example the abstract).

With respect to claim 31, Bronstein et al. teach a wash step prior to addition of the substrate composition (column 10, line 59 to column 11, line 2; column 13, lines 36-39).

With respect to claim 39, it would have been further obvious to include BSA as an additive because Voyta et al. teach that these compounds, like quaternary onium polymers, also serve to enhance the chemiluminescent signal. It would have been similarly obvious to further include polyvinyl alcohol (which is both an alcohol and a polyol) because Voyta et al. teach that this may be additionally used along with quaternary ammonium salts (see column 5, line 65 to column 6, line 23).

With respect to claim 40, Voyta et al. teach that the polymeric enhancer substances also include a counterion moiety such as halide, sulfate, arylsulfonate, alkylfulfonate, and combinations thereof (see in particular column 4, right column, the structure and line 64 to column 5, line 10).

With respect to claims 44-45, the compound poly(vinyl-benzyltrimethylammonium) chloride taught by Voyta et al. is an onium copolymer ("poly") as well as a poly(vinylbenzylammonium) salt.

20. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. and Voyta et al. as applied to claim 6 above, and further in view of Ferea et al. (US 6,905,826).

Bronstein et al. and Fodor et al. (discussed above) teach control probes, but fail to specifically teach that the control probes are located in one or more of the same discrete areas as probes for a target molecule.

Ferea et al. teach methods for detecting target molecules in a sample using microarrays, and in particular, controls to be used in such methods in order to allow for correction of irregularities in the shape, size, and intensity of microarray features (column 5, lines 49-52). Control signals can also be used to quantify the experimental signal (column 6, lines 16-19). Control oligonucleotide probes may be deposited onto the array in the same discrete areas ('features') as the experimental probes in order to serve as hybridization controls (column 6, lines 41-60; claim 1 and Figure 4 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art to employ control probes located in the same discrete areas as the experimental probes as taught by Ferea et al. in the method of detecting chemiluminescent emissions of Bronstein et al., Fodor et al., and Voyta et al. in order to act as an experimental control to determine whether hybridization is occurring. One would have a reasonable expectation of success because Ferea et al. relates to

methods of detection based on nucleic acid hybridization using microarrays, which is the same format of Fodor et al.

21. Claims 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. and Voyta et al. as applied to claims 11 and 14 above, and further in view of Akhavan-Tafti et al. (US 6,068,979).

Bronstein et al. and Fodor et al. (discussed above) teach samples comprising targets that may be pools of nucleic acids and that may be labeled with enzymes. Fodor et al. also teaches indirect labeling of the targets, for example by labeling of the targets with biotin (see especially column 1, lines 3-24).

However, the references fail to specifically teach that the target molecules are indirectly labeled with *digoxigenin* or that the enzyme conjugates are *antidigoxigenin:enzyme* conjugates.

Akhavan-Tafti et al. teach binding pairs, including antigen-antibody and biotin-avidin or streptavidin interaction that may be used in labeling molecules with enzymes for chemiluminescent detection. One member of a binding pair may be attached to an enzyme in order to form an enzyme conjugate, which is then capable of interacting with a target molecule labeled with the other member of the binding pair (column 4, lines 30-40 and column 5, lines 18-28). Specific examples of antigen-antibody binding pairs include antidigoxigenin-digoxigenin, where antidigoxigenin-enzyme conjugates are used as the enzyme conjugate (columns 15-16, Example 2, and Figure 3).

Therefore, it would have been obvious to one of ordinary skill in the art to indirectly label the target molecules with digoxigenin followed by labeling with an antidigoxigenin-enzyme

conjugate as taught by Akhavan-Tafti et al. in the method of Bronstein et al., Fodor et al., and Voyta et al. because Akhavan-Tafti et al. teach that both biotin-avidin (taught in Fodor et al.) and the digoxigenin-antidigoxigenin are binding pairs that can be used for indirectly labeling nucleic acids, which is the same purpose for which the biotin-avidin system is used in Fodor et al. It would have been further obvious to employ the digoxigenin-antidigoxigenin system of Akhavan-Tafti et al. in order to label the pool of target nucleic acids that are cDNA since cDNA is one type of nucleic acid sample that may be indirectly labeled and detected in Fodor et al. (see column 17, line 56 to column 18, line 8).

One would have a reasonable expectation of success because Fodor et al. teaches indirect labeling generically; although Fodor et al. provide the example of biotin-avidin, there is no indication that the indirect labeling is intended to be restricted to this binding pair. One would also have a reasonable expectation of success because both Akhavan-Tafti et al. and Fodor et al. teach indirect labeling of nucleic acids with labels that may be enzymes.

22. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. and Voyta et al. as applied to claim 1 above, and further in view of Oldham et al. (US 6,970,240 B2).

Bronstein et al. and Fodor et al. (discussed above) teach a method of detecting chemiluminescent emissions on a solid support (microarray), but which fail to specifically teach that the support surface further comprises a fluorescent control.

Oldham et al. teaches an apparatus for imaging an array using fluorescent or chemiluminescent detection (column 1, lines 1-58). In particular, Oldham et al. teach that at least

some of the discrete areas ("feature") of the solid support (sample tile 42) may include a fluorescent marker (see also column 2, lines 18-58). The fluorescent signals generated allow for auto-focusing of the array, to allow for the size and shape of each feature in the array to be easily determined, and to normalize the chemiluminescent signals (column 3, line 55 to column 4, line 32). A normalizing fluorescent image is first collected, followed by detection of chemiluminescent signals (column 7, line 20 to column 8, line 51).

Therefore, it would have been obvious to one of ordinary skill in the art to include a fluorescent marker in the microarray solid support of Fodor et al. in order to allow for normalization of chemiluminescent signals in the method of Bronstein et al., Fodor et al., and Voyta et al. One would have a reasonable expectation of success because Oldham et al. teach that the apparatus is intended to be used in detection methods using nucleic acid microarrays and chemiluminescent signals, which also describes the method of Bronstein et al., Fodor et al., and Voyta et al.

Response to Arguments

23. Applicant's arguments filed 3/14/07 have been fully considered.

24. Applicant's arguments with respect to the rejections under 112, 2nd paragraph are acknowledged (see page 9) but are moot in light of the new grounds of rejection set forth above.

25. Applicant's arguments with respect to the rejections over Bronstein in view of Fodor, and over Bers in view of Fodor, are acknowledged (see pages 10-11) but are moot in light of the withdrawal of the rejections as noted above.

26. With respect to the rejections under 35 USC 103(a) over Bronstein in view of Fodor and Voyta, Applicant's arguments (see pages 11-12) have been considered but are not persuasive. Applicant argues that there is objective evidence of non-obviousness and points to a declaration under 35 USC 132 submitted in copending application No. 10/620,332 (a copy of the declaration has been submitted with Applicant's amendment). As best understood, Applicant is arguing that the Declaration provides evidence of non-obviousness due to *unexpected results* (see the Declaration at page 4).

The Declaration under 37 CFR 1.132 filed 3/14/07 is insufficient to overcome the rejection of claims 2, 39-40, and 44-45 based upon Bronstein in view of Fodor and Voyta applied under 35 USC 103(a) as set forth in the last Office action (now applied to claims 1, 3-6, 9-11, 15-26, and 28-32, 39-40, and 44-45 above) for the following reasons.

Applicant has not established that the property or result is actually unexpected

In the instant case, Applicant argues that the Declaration shows "significant improvements in assay performance" due to the use of "an onium polymer or copolymer chemiluminescent enhancing material and a chemiluminescent 1,2-dioxetane substrate in a microarray format on a two-dimensional support" (Applicant's reply, see the paragraph bridging pages 11-12). The Declaration describes a substantial difference in chemiluminescent signal in the presence of "TPQ polymer enhancer" as an example of a chemiluminescent enhancing material.

However, *expected* beneficial results are evidence of *obviousness* of a claimed invention, just as unexpected results are evidence of unobviousness thereof. In re Gershon, 372 F.2d 535,

538, 152 USPQ 602, 604 (CCPA 1967) (see also MPEP 716.02). In the instant case, Voyta et al. clearly teach that the chemiluminescent enhancing materials have the effect of enhancing or increasing chemiluminescent signals (see especially column 2, line 5 to column 3, line 7). Similarly, Akhavan-Tafti (US 6,068,979, of record), also teach that chemiluminescent quantum yield enhancing materials (including the claimed onium polymers) are known to enhance chemiluminescent signals (column 10). The materials are specifically termed "enhancers" by Voyta et al. and Akhavan-Tafti et al. as a result of their known property of *enhancing* chemiluminescent signals.

Therefore, the experiment in the Declaration documenting increased chemiluminescent signal due to the use of a chemiluminescent quantum yield enhancing material is not persuasive to establish non-obviousness, since such enhancing materials were known in the prior art to increase chemiluminescent signal, as taught for example by Voyta et al. and Akhavan-Tafti et al. above. Given that the use of such onium polymers would in fact be *expected* to improve the chemiluminescent signal, the Declaration is insufficient to demonstrate unexpected results because the property or result must actually be unexpected. *In re Skoll,* 187 USPQ 481, 484; *In re Coleman,* 205 USPQ 1172.

The Declaration is not commensurate with the scope of the claims

In addition, the Declaration is ineffective because the scope of the showing must be commensurate with the scope of the claims. *In re Coleman,* 205 USPQ 1172; *In re Greenfield,* 197 USPQ 227; *In re Lindener,* 173 USPQ 356; *In re Payne,* 203 USPQ 245. The Declaration relates to the use of a single 1,2-dioxetane substrate (TFE-CDP-Star®) (and a single enzyme

conjugate), while the instant claims are drawn to the use of a composition comprising two 1,2-dioxetane substrates. As such, the Declaration does not depict the claimed invention. Further, the Declaration is not commensurate with the scope of the claims because the claims are drawn to any two 1,2-dioxetane substrates, while the Declaration pertains only to TFE-CDP-Star®.

Further, the Declaration is not commensurate with the scope of the claims because the claims are drawn to any onium polymer or onium copolymer as the quantum yield enhancing material, while the Declaration pertains only to the use of "TPQ polymer enhancer" (see p. 2 of the Declaration at item 7), which does not even appear to be an onium polymer or copolymer (as required by claim 1). It is noted that the Declaration does not specifically identify this material as an "onium polymer or copolymer". As such, there is nothing of record to show that the "TPQ polymer enhancer" used in the experiment of the Declaration would even represent a species reading on the claimed genus of a composition comprising an onium polymer or an onium copolymer.

Rather, the prior art teaches that "TPQ" stands for 1,3,4-tris[3-phenyl-6-trifluoromethyl]quinoxaline-2-yl)benzene (see Woo et al., US 20020061419 A1, see [0065]). Since "TPQ" itself lacks any "onium" groups or substituents, the "TPQ polymer" used in the experiment of the Declaration fails to provide evidence of unexpected results associated with the use of onium polymers or copolymers as enhancing materials since the Declaration does not describe the use of any "onium" polymers or copolymers.

Furthermore, the Declaration also pertains only to solid supports that are *film*, while the claims are broadly drawn to any *two-dimensional solid support*. The Declaration also describes *overcoating* a high-density array with the TPQ polymer, while the claims relate only to

contacting the chemiluminescent substrate *in the presence of* an onium polymer or copolymer, which would include various means of simultaneous contact other than overcoating the support itself.

For all of these reasons, the Declaration is insufficient to demonstrate unexpected results there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

27. Claims 1, 3-6, 8-11, 14-31, and 39-45 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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